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DIOXIN

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News of the Week

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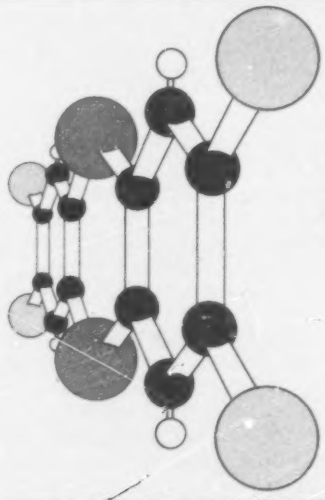

DIOXIN REPORT

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, though found in minute quantities, has made a giant impact as a potential hazard. **Page 20**

History

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Dioxin Issue Focuses on Three Major Controversies in U.S.

Furor developing around the question of dioxin exposure has reached a head in three historic cases—agent orange, Times Beach, and Tittabawassee River

Janice R. Long,
David J. Hanson,
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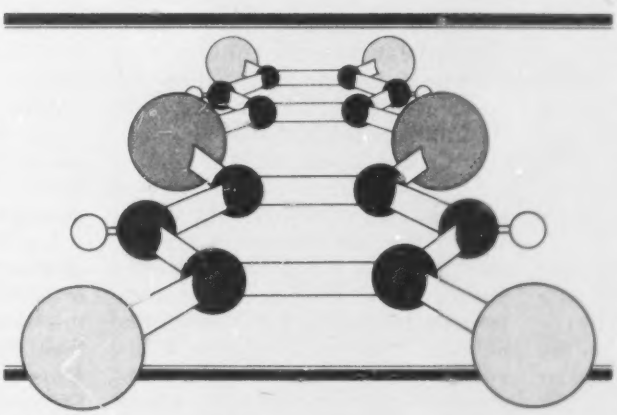

When the history of human problems with exposure to toxic chemicals is discussed in the years to come, one of the principal topics of debate will be the effects of the compound called dioxin. And, in that debate, if it focuses on the U.S., three names will be recalled—agent orange, Times Beach, and the Tittabawassee River.

More than any other incidents, these three widely differing examples of dioxin exposure point out the problems our scientific, regulatory, and legal systems have in handling the undefined hazards of potentially very dangerous substances.

Central to the entire problem is the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Developed during World War II, it was first registered in the U.S. as a pesticide March 2, 1948, and it has been the subject of considerable study ever since.

There were some health problems associated with 2,4,5-T almost from the beginning. In 1949, an industrial accident at a Monsanto plant in Nitro, W.Va., exposed 250 workers to the compound, with a number of resulting illnesses. But it wasn't until about 1955 that the cause of the illnesses, mostly the severe skin rash called chloracne, was found. West German physician Karl Schulz, treating workers from a Boehringer Ingelheim pesticide plant in that year, identified 2,3,7,8-tetrachlorodibenzo-*p*-dioxin as the cause of the chloracne. Schulz's work was published in West Germany in 1957, and appeared in *Chemical Abstracts* in December 1958.

Still, despite this problem, 2,4,5-T was considered a good herbicide and its use spread. It was used extensively on rangeland and pastures to kill unwanted weeds, and also on rice and nursery crops. Because 2,4,5-T is quite biodegradable and works so well, it, as well as other herbicides (particularly 2,4-dichlorophenoxyacetic acid) was considered by the military in the early 1960s as the best means of defoliating large sections of forest in Vietnam to take away cover from the enemy.

Spraying began in Vietnam in January 1962, using a variety of herbicide concoctions. Only small amounts were used at first, but the amounts jumped at the end of 1965 and heavy use continued until 1969, when mounting concerns about damage to Vietnam's ecology led to a tapering off and finally a halt to the spraying of 2,4,5-T in 1970. Of the seven or so herbicide formulations used, the most significant was called agent orange, an oily liquid that was a 50-50 mixture of the *n*-butyl esters of 2,4,5-T and 2,4-D.

However, because the 2,4,5-T was contaminated with dioxin, and because during this time it was discovered that dioxin is frighteningly toxic in some animals, and because an unknown number of U.S. personnel were exposed to the herbicide while in Vietnam, an exceedingly complex problem has arisen.

Vietnam veterans, learning from press accounts during the 1970s that dioxin was hazardous and that they might have been exposed, began to ask the Veterans Administration some tough questions. The Chicago VA office really started things moving when a case worker there asked veterans about their possible exposure to agent orange and any subsequent illnesses. She compiled a list of apparently affected veterans that

found its way into the hands of a local news producer who made a documentary pointing out the possible connection.

As a result of the fears raised by this and other accounts, VA reports that as of May 1 of this year, 17,068 veterans have put in claims for disability payments because of agent orange exposure, and VA hospitals have treated 369,000 outpatients and hospitalized 9600 veterans who claim their medical problems are related to dioxin exposure. (These numbers also included a relatively small number of veterans seeking help because of radiation exposure during early atomic bomb tests.)

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The problem, according to VA, is that it has essentially no evidence that the variety of complaints being described by the veterans had anything to do with exposure to agent orange or its dioxin contaminant. Consequently, VA has balked at offering compensation.

Part of VA's reason for rejecting the agent orange connection is a large amount of data compiled by the Air Force in the early 1970s on the use and fate of the herbicide and its contaminant, dioxin. This work finds, in general, that the herbicide, when sprayed on the top of a forest, quickly was destroyed by sunlight; that very little penetrated through the forest canopy to the ground; and that if it did get into the soil, the dioxin stayed there.

But the growing cries from veterans groups that their problems were caused by agent orange prompted others to act. Seeking some hard information on the potential problems from agent orange exposure, Congress passed a law at the end of 1979 that required VA to do an epidemiology study of Vietnam veterans and to compile a complete bibliography of 2,4,5-T and dioxin health studies. VA also began an agent orange registry, an effort to identify all veterans concerned about exposure to agent orange and find out what health problems they are experiencing. Veterans' records are computerized for future work.

The biggest problem VA has had is getting the epidemiology study under way. Plans to contract out design of the study to the University of California, Los Angeles, School of Public Health were countered by a lawsuit from the National Veterans Law Center. Lewis Milford of the center says veterans did not believe VA would do an objective job in analyzing the data, because of a prejudice against blaming agent orange. Subsequently, bowing to pressure from the House Veterans Committee Subcommittee on Oversight & Investigations, as well as other Congressmen, VA transferred the whole epidemiology study to the Center for Disease Control.

Still, this did nothing for the growing number of veterans who wanted medical attention for problems they assumed were caused by the herbicide. In 1981, Congress passed the Veterans' Health Care, Training & Small Business Loan Act, which, in part, changed the rules for treatment at VA hospitals so that medical treatment for agent orange claims could be provided. Although this means most veterans who want it can get some medical attention, the question of disability compensation has not been resolved.

For veterans groups, the disability compensation issue is a top priority. According to Milford, there is enough medical evidence of a link between dioxin and cancer to allow VA to make payments. But VA claims the only confirmed medical problem is chloracne and VA has yet to grant the first disability claim for agent orange exposure.

Not that veterans haven't tried. As of May 1, 17,068 claims had been filed by persons who say they have been exposed to agent orange. Some 8400 were found to have a valid medical complaint and 1328 claims have been honored, but for reasons other than agent orange exposures. According to VA, 8617 of the claimants, when examined, had no diagnosable illness. In fact, 4102 did not even have a medical complaint, diagnosable or not.

To break this impasse, Rep. Thomas A. Daschle (D.-S.D.) has introduced legislation that would make any veterans suffering from chloracne, soft-tissue sarcoma, or the liver condition called porphyria cutanea tarda automatically eligible for compensation, whether or not any link to agent orange exposure could be made.

It is hoped that the large number of research programs now under way or starting soon will help answer all the various questions. There are at least 65 federally supported programs, expected to cost more than $100 million, in the works to study dioxin. The largest of these is the epidemiology study being done for VA by CDC. This will involve 30,000 people divided into five cohorts and will be looking for any health problems that could be associated with military service in Southeast Asia. The study is not expected to be completed until late in 1987, but other work will be finished earlier.

One of the first is the Ranch Hand study by the Air Force of about 1200 military personnel who worked spraying agent orange on South Vietnamese forests. A mortality study of these individuals has shown no evidence of a problem one way or the other, but the sample size is far too small to mean anything. More significant will be the morbidity analysis of these people that is expected this fall.

Another VA mortality study will gather data on all veterans who served in Vietnam from 1964 to 1975

and compare their cause of death with that of veterans who were not stationed there. A twins study is also part of the VA program. About 500 pairs of twins have been found, one of which served in Vietnam and the other did not. They will be given psychological, physiological, and biochemical tests to see if any health differences can be found.

VA also is utilizing the Environmental Protection Agency's National Human Adipose Tissue Study, which has been examining human fat tissue since 1972 for the presence of about 20 chemicals, but not for dioxin. VA plans to backcheck 550 samples available from men born between 1937 and 1952 who could have served in Vietnam. VA does not expect to finish this analysis until 1985. However, under the direction of Alvin R. Young, an Air Force scientist who has been involved with agent orange studies since 1969, a small pilot study of fat tissue from exposed veterans already has been done. It casts some doubt on the ability of this kind of analysis to detect any connections between illnesses and dioxin exposure.

Then there is the chloracne task force, a major effort by VA to find veterans who have the one health problem that has been confirmed as dioxin related. But to date, about 4300 claims of skin disease have been made, and only 13 could be considered service related by VA and only one of those appeared to be truly chloracne.

Another large project that has just begun at VA is a case-controlled epidemiology study for possible occurrence of soft-tissue sarcomas. These cancers, usually very rare, have been linked to dioxin exposure by two Swedish studies and some U.S. industrial experiences. About 1000 soft-tissue sarcomas recorded at the Armed Forces Institute of Pathology involve men aged 25 to 40 who might have been in Vietnam when the spraying was done. Although the protocol still is being developed, final results are expected by the end of 1985.

These federal programs are only part of the work under way. Most were started only in the past couple of years when it was realized that huge potential problems related to dioxin exposure existed. Several states have set up their own task forces to help veterans, and there are many international investigations that are trying to find a link between the phenoxy herbicides and a variety of health problems.

Veterans with disabilities they believe were caused by exposure to dioxin in Vietnam quickly learn that unless they get compensation from VA, no other government aid will be forthcoming. There is a strong feeling among many of these veterans that the government has a responsibility not to expose its people to hazardous substances, and that, if it does so, it should be liable. But there is a long history of the courts refusing to allow veterans to sue the government for this type of injury. So, attention has been turned to the companies that manufactured the herbicides that became agent orange.

In 1979, Victor J. Yannacone Jr., representing the survivors of a helicopter pilot who served in Vietnam, sued 11 companies for their part in exposing veterans to toxic chemicals. The number of plaintiffs has since climbed to about 9000, including 5000 veterans and 4000 survivors and children of veterans. The suit insists that the companies knew of the toxicity of agent orange's components

Dioxin history at a glance

1872 Chlorinated dioxins first synthesized by German chemists.

1948 2,4,5-T registered as a pesticide with U.S. Department of Agriculture.

1949 First industrial accident involving dioxin at Nitro, W.Va., 2,4,5-T plant.

1957 Dioxin identified as an unavoidable contaminant in 2,4,5-T.

1962–70 2,4,5-T used in defoliants in Vietnam.

1966 U.S. Department of Agriculture and Food & Drug Administration established residue tolerances for 2,4,5-T on food products.

1970 Dioxin's teratogenicity, fetotoxicity first reported in animals.

U.S. Department of Agriculture suspends uses of 2,4.5-T that might lead to greatest human exposure.

1971 Environmental Protection Agency cancels 2,4,5-T use on most food crops.

Stables in eastern Missouri sprayed with dioxin-contaminated oil.

1972 FDA bans use of hexachlorophene in nonprescription soaps and deodorants.

1973 Vietnamese study links higher incidences of liver cancer, abortions, and birth defects to agent orange spraying in that country.

1976 Explosion at ICMESA chemical plant in Seveso, Italy, releases several pounds of dioxin in a densely populated area

1978 EPA issues rebuttable presumption against registration for remaining uses of 2,4,5-T based on evidence that 2,4,5-T and dioxin cause cancer, birth defects, and fetal deaths.

1979 Environmental Protection Agency issues emergency suspension order to ban remaining 2,4,5-T uses except on rangeland and rice fields.

Class action suit filed on behalf of Vietnam veterans against five U.S. chemical companies that made agent orange. Companies, in turn, file a third-party action against the U.S. government passing responsibility for alleged harm to the government for its negligent misuse of the chemicals.

1980 EPA requires advance notice of disposal of dioxin-contaminated waste.

1981 Class action suit on behalf of Vietnam veterans filed against Veterans Administration and Department of Defense.

FDA advises people not to eat fish containing 50 ppt or more of dioxin.

1982 Extensive dioxin contamination found in eastern Missouri.

1983 EPA offers to buy the town of Times Beach, Mo.

EPA issues proposed rule allowing disposal of dioxin-contaminated wastes only in approved landfills.

and failed to inform the government and that, therefore, the companies should be liable for injuries caused by the herbicide and the dioxin contaminant. The suit has become lengthy, complex, and costly.

The original companies named were Dow Chemical, Monsanto, Hercules, Thompson-Hayward, Uniroyal, Diamond Shamrock, Thompson Chemical, Aggrasit, Hoffman-Taft, Riverside Chemical, and Hooker Chemical (which made the 2,4,5-T precursor 2,4,5-trichlorophenol).

Most of the companies asked U.S. Federal District Court judge George Pratt for a summary dismissal of the claims that they are responsible for any injuries, under the government contractor defense. This means that the government, as the user of the herbicides, knew as much as or more than did chemical companies about the hazards and should have used this knowledge to warn those who might be exposed. They also contend, and have proved to the judge's satisfaction, that the Department of Defense had set standards for agent orange which were met by all the companies. Two companies that have not asked for a summary judgment are Monsanto and Diamond Shamrock.

For a variety of reasons, some of the companies have been released from the suit. Those remaining are Monsanto, Diamond Shamrock, Uniroyal, Thompson-Hayward, and the largest producer, Dow. The trial had been scheduled to begin June 27, but, in a procedural move, Pratt postponed the opening until completion of the discovery process, an information gathering period that attorneys say could take another year or two.

The judge's decision to go ahead with the trial means that the companies must prove they withheld no health data from the government that would have made a difference in the spraying of the herbicide. Although there are some data in the early work on 2,4,5-T on the problems from dioxin, they are scanty. Dow, which made more than 30% of the total agent orange used in Vietnam, is sure the government had all the safety data it needed.

One of the allegations raised against the companies stems from a meeting in 1965 between Dow and other agent orange makers in which the toxicity of dioxin was discussed. Dow is supposed to have told the manufacturers they would have to do something about the levels of dioxin in agent orange, or the government would take regulatory action against the use of 2,4,5-T. Shortly after that, Dow bought a license to use a process developed by West Germany's Boehringer Ingelheim that reduced levels of dioxin in 2,4,5-T to less than 1 ppm and urged the other makers to do the same. According to Dow, some did and some did not. Whether the 1-ppm level is a safe one for dioxin is one of the questions that has not been answered, though that is just what the jury may be asked to decide at this trial.

If the companies are found liable for the injuries allegedly resulting from dioxin exposure, they can be sued in state courts by veterans or their survivors for damages. In most states, the statute of limitations will have expired for taking action against the companies and special legislation will have to be passed, as it has been in New York for instance, if the veterans are still going to be able to sue over agent orange exposures.

Just how many vets actually were exposed is a question impossible to answer. The military records are not accurate enough to tell exactly where every soldier was when spraying was done in an area. And wind drift or elapsed time before troops entered a sprayed area also would determine exposure. DOD had said early in the agent orange controversy that it kept troops out of sprayed areas for up to six weeks, but many reports show that gound troops entered some sprayed areas as early as the next day. Veterans groups say they have anecdotal evidence that planes sprayed some troops directly, or that troops had loads of agent orange dumped on them when a plane was damaged by enemy fire and had to return quickly to its base.

Despite the controversy over exposure and possible health problems, VA still holds that no long-standing health problems exist from agent orange exposure. It appears, however, that this position is being eroded by the actions of other federal agencies in response to dioxin contamination, and the difference has not been lost on veterans. Although most regulatory action against 2,4,5-T and its contaminant dioxin was not begun until after 1970—after most troop exposure in Vietnam was past—concerns about health effects of dioxin from agencies such as EPA and CDC appear to be far greater than those voiced by officials at VA. Nothing makes this clearer than the dramatic actions taken to remedy the dioxin contamination problem in Times Beach, Mo.

Times Beach has a most unenviable reputation as the town too poisoned to live in. Just a few miles west of St. Louis, its fate has been sealed as the result of some poor waste disposal practices, insufficient environmental laws in the early 1970s, and political pressures for action. Because of the contamination and the federal government's decision to buy the town, Times Beach is expected to disappear.

The story traces back to the 1960s and begins with agent orange. Hoffman-Taft, one of the original defendants in the agent orange trial, made 2,4,5-T for the Department of Defense for a while, but ceased production in 1969, about the time ecological concerns led the military to halt spraying. In November of 1969, the plant in Verona, Mo., was leased to North Eastern Pharmaceutical & Chemical Co., and then later sold to Syntex Agribusiness, which let the pharmaceutical company stay to produce hexachlorophene.

According to EPA's records, wastes from the plant were being disposed of properly by shipping them to a waste facility owned by what is now Rollins Environmental Service near Baton Rouge. But in early 1971, allegedly to save money, North Eastern contracted with a firm called Independent Petrochemical to haul away its sludge bottoms. Independent, in turn, subcontracted the job to Russell Bliss, a waste oil hauler in Missouri. The records show that Bliss hauled away 18,500 gal of waste bottoms containing dioxin from the Verona plant, which he apparently stored in waste oil tanks near Frontenac, Mo., between February and October 1971.

But Bliss used some of this contaminated waste oil to spray horse arenas in May of 1971. Three stables apparently were sprayed, and the consequences were severe. Over the next few days and weeks, hundreds of animals got sick and died, including at least 65 horses. One six-year-old child, the daughter of one of the stable owners, developed an inflamed and bleeding bladder after playing in the soil of the arena, and three other children and one adult complained of skin lesions after exposure to the stables. All the symptoms disappeared after exposure was halted and have not recurred.

State of Missouri investigators, reasoning that something must have been in the oil that was sprayed, sent samples to CDC for analysis. The arena owner asked Bliss if anything dangerous had been in the oil and Bliss reportedly said there was not. In the meantime, the state had the arena's dirt hauled away and placed in a distant landfill. Some of it, however, was used as fill dirt for residential construction, in what has now become known as the Minker/Stout site.

CDC, with few clues to go on, took until 1974 to identify dioxin as the toxic compound in the oil. Scientists there, led by pathologist Renate Kimbrough, eventually determined that the oil was contaminated at about 33 ppm, a level far higher than any that occurred in Vietnam from agent orange. Crystals of trichlorophenol found during the soil analysis extraction led the investigators to the Hoffman-Taft plant in Verona, and the thinking was that 2,4,5-T production was the culprit. But it was then discovered that the hexachlorophene wastes made by North Eastern had been disposed of improperly.

By this time, Bliss had sprayed oil over many sites in eastern Missouri. EPA has reconstructed as much of the Bliss operation as possible and believes there were more than 150 sites sprayed with the waste oil, but how many are contaminated with dioxin won't be known until testing can be completed.

The search for contaminated areas did not begin immediately, however, as might have been expected. A large storage tank of wastes was found at the Verona site, heavily contaminated with dioxin. Levels of extracts were measured at 356 ppm by the CDC researchers. This became the primary concern because its potential for human health injury was seen as high. Syntex, which now owned the plant, had the wastes detoxified by ultraviolet treatment at its expense. It should be remembered that at that time there were no federal laws governing waste cleanup or proper disposal. The Resources Conservation & Recovery Act was not passed until 1976, and the abandoned waste cleanup law, superfund, didn't go into effect until 1981.

With no further reports of serious illnesses, the issue faded away after about 1975.

Then, in 1979, EPA's office in Kansas City received an anonymous telephone call that toxic wastes were buried on the James Denney farm, near Verona. The tip checked out, and a number of drums of dioxin-contaminated waste eventually were removed from the site. This got EPA investigators thinking.

It had been believed in the early 1970s that the half-life for degradation of dioxin in soil was less than a year, based on tests by the Air Force and U.S. Department of Agriculture. That was wrong. EPA found that waste leakage from the drums still had high concentrations of dioxin, when almost all of it should have decomposed after being buried for six or seven years. This prompted them, after much record searching, to go back to the stables that originally were sprayed and to the sites where the contaminated earth was dumped to measure present dioxin levels. The levels found were essentially as high as they had been in 1971. At the site where the soil had been used as a landfill, levels ranged from 10 ppb to 300 ppb. At the Shenandoah Stables, concentrations were still as high as 1750 ppb.

These tests began in spring of 1982, and the first data were released in August. The findings prompted a more exhaustive sampling of all the areas known to have been sprayed. By December, more than 300 samples had been analyzed and the results released. EPA had found dioxin levels of up to 300 ppb in the Times Beach area and contamination in about 14 other sites.

The news of extensive dioxin contamination in Missouri came at a critical time for the agency. EPA Administrator Anne Gorsuch Burford was under intense pressure from Congress for information relating to actions the agency had or had not taken under the superfund law, and that body was moving in early December towards finding Burford in contempt of Congress. The situation was complicated when the Meramec River, which flows by Times Beach, flooded just before Christmas 1982, and officials worried about the dioxin spreading to other communities. (Followup tests showed that the dioxin had not moved with the flood waters.)

Trees (upper left) in this part of Vietnam were defoliated with 2,4,5-T

The situation now began to get tense. Residents of the community demanded that the government buy their homes so they could move to a safe place. Some people began comparing the contamination problem at Times Beach to the situation at Love Canal in New York. Then, in early February, the EPA assistant administrator in charge of waste cleanup and superfund, Rita Lavelle, was fired by President Reagan, amid allegations she had used the superfund for political leverage in favor of Republican candidates.

Possibly pushed a little faster than she would have been otherwise, EPA Administrator Burford announced Feb. 22 that the federal government would buy up all the contaminated property in Times Beach, paying the residents a price reflecting property values before the dioxin contamination was found and before the flooding. Superfund would supply $33 million and the state of Missouri would supply $3.3 million more.

Subsequently, on April 5, EPA offered to buy a number of homes in the contaminated Minker/Stout site that had been built on dirt from the stables originally sprayed by Bliss. A third area, the Quail Run mobile home park, was found to be contaminated with up to 1100 ppb of dioxin in a sample dug out from beneath a paved road, with levels of 2 ppm inside two of the mobile homes. EPA has also offered to buy the trailer park. At this time, no other areas are being bought out.

The decision to move residents, either temporarily or permanently, is made by CDC and the Missouri Department of Public Health, on the basis of results from samples submitted by EPA. The belief that a level of 1 ppb is probably safe comes from a CDC estimate using a number of studies, and is discussed on page 48.

When EPA told the residents of Times Beach the government was going to buy their homes, the process was expected to take 60 to 90 days. Now, after three months, there is still a hangup. The federal government cannot take title to the property because the law forbids spending superfund money to clean up federally owned property. Missouri will not take title until all the residents have moved because they do not want to be expected to provide services, such as water, to the areas. There were, last month, about 50 families that were not moving, but a second flooding of the Meramec seems to have convinced them it was time to leave. Spokesmen for the Federal Emergency Management Administration, which has been on the site since the first flood in December and is responsible for dealing with the residents on the buyout, say it appears that all the former residents are leaving. In addition, an unofficial and unapproved agreement may have been reached that would permit the property to first be assigned to the city of St. Louis, so the cleanup could get started, then transferred to Missouri when that state's conditions are met. In the meantime, the residents are living elsewhere and have yet to receive the promised compensation.

As of this writing, there are 31 confirmed sites of dioxin contamination in eastern Missouri, all traceable to the spraying by Russell Bliss. Officials believe the final list could contain more than 100 sites. How many more people might have to be moved and how much it will cost is pure speculation, but the expenses can be expected to rise.

Midland, Mich., is another city that has become associated in the public mind with dioxin contamination.

The Midland connection first surfaced in the national news media last March when Rep. James H. Scheuer (D.-N.Y.) charged that he had evidence showing that then EPA acting administrator John Hernandez had intervened personally to allow Dow Chemical Co. to alter a draft EPA report on the sources and effect of dioxin in the Great Lakes region, suppressing all references to Dow's responsibility for dioxin contamination in and around its plant.

In fact Scheuer charged that owing to Hernandez's intervention, and by implication Dow's, all references to studies showing the adverse health effects of dioxin were removed from the report.

Testifying before Scheuer's natural resources subcommittee on March 23, Valdas Adamkus, EPA's Region V administrator, said that Dow's

C&EN staff photo

Young: doubt cast on ability to link illness with exposure to dioxin

objections to the draft report centered on a statement that EPA concludes that Dow's Midland facility is a major, if not the only source, of dioxin contamination in the Tittabawassee and Saginaw Rivers and Saginaw Bay in Michigan. That six-line draft conclusion did not appear in the final report.

Ronald O. Kagel, director of environmental quality for Dow Chemical USA, who reviewed the report for EPA, says, emphatically, that he did not ask EPA to delete that six-line paragraph from the report. He says he did point out that "the whole paragraph was lifted out of a 1978 report and it appeared again almost word-for-word in a report written in 1979. At that time we could not dispute that and we didn't. But in 1981 there had already been an international dioxin conference. There had been many papers published supporting our theory that dioxin can be created by combustion. I said, 'Gee guys, that's a 1978 statement in a 1981 report and I really think you should change the word 'concludes' to 'speculates' because of the data that support our theory.' "

Kagel says that in making his comments he was "strictly trying to

speak to the validity and technical accuracy of the report and specifically those portions that were taken out of Dow's work." Further, he says that many of the portions of the draft report released by Scheuer that were marked "cut" already had been deleted from the copy of the report he received. Others had markings indicating that somebody already had decided they should be cut.

At just about the time the charges of undue influence were being aired two Michigan environmental groups—the Foresight Society, headquartered in Lansing, and the Environmental Congress of Mid-Michigan, headquartered in Midland—filed a citizens petition with EPA asking for a full field investigation of central Michigan. They said an investigation was needed to determine the effect of the pollution caused by disposal and emissions into the air, land, and water of chemical substances that threatened the health of the residents and the integrity of the environment. At a press conference in Washington, D.C., Andrea K. Wilson, director of ECOMM, explained that "given the fact that soft- and connective-tissue cancers among white females in Midland County are four times the national average, the birth defect rate is now being re-evaluated, and Dow's own data indicate that soil samples taken at their Midland plant contain a range of TCDD (dioxin) from 0.3 ppb to 100 ppb, we feel that a full field investigation, including an epidemiological study, is warranted."

Hard on the heels of the petition came an announcement by EPA's Region V office (which covers the upper midwest) that a preliminary investigation had found more than 40 toxic chemicals, mostly in the low parts-per-billion range, in the effluent from Dow's Midland facility. Dioxin was found at levels of 50 parts per quadrillion in the effluent and at levels of 100 ppt in caged whole fish that were exposed to the effluent.

The search for dioxins in Midland may very well have been initiated by a false-positive test result. Dow periodically monitors its discharges for TCDD and on April 13, 1977, the lab reported a positive number—8 ppt with a detection limit of 3 ppt. "That got us concerned," Kagel explains, "because we had never seen dioxin before . . . but it triggered a number of things." The first thing that was done was an analysis of some fish that had been caught in the Tittabawassee River the year before during Dow's biennial river survey and placed in the freezer. Analysis of the fish showed dioxin levels ranging from nondetectable to 0.19 ppb, with a detection limit of 0.02 ppb. In May of 1977 the company collected more fish—mostly bottom feeders—from the river, analyzed them, and again found positives. Kagel points out that the state-of-art analytical method at that time allowed only the detection of 2,3,7,8-TCDD, plus 16 other tetra isomers.

After the second batch of fish was analyzed, Dow devised some experiments using caged fish to determine where the dioxin was coming from. The first shipment of fish ordered died before it got to Dow. The second batch of fish all had a fatal fish disease, commonly known as the "Ick." The third shipment from the East was found to be loaded with PCBs, which would have interfered at the time with the TCDD analysis. Finally, towards the end of 1977 Dow got a batch of usable trout and put them in cages where its effluent mixed with the river water under flowing conditions. Bioanalysis of the caged fish was completed in May 1978. Positives were found for most fish in the mixing zone. At the same time, Kagel says the fish research lab, which had been doing studies on the biomagnification of TCDD by trout, reported a biomagnification factor of 6600. Dow reported all of its findings to the State Department of Natural Resources in June of 1978. In July, the company met with state representatives and made a commitment to find the source of the dioxins.

The first thing Dow did, Kagel says, was to look at its own internal waste streams, where it might expect to find dioxins, and didn't find anything that could be considered significant. Then, he says, "Quite by accident two of the chemists in the lab went up to the second floor to get a control sample of dust off a bookshelf. They analyzed that dust and found it contained all the dioxins—the tetras, the heptas, the hexas, the octas. We said, 'My God, we've been looking for a waterborne source and we know that . . . the second floor has never been under water. So it's got to be from somewhere else that's airborne."

That, he explains, is when "we started looking around the division at dirt samples and seemed to find more dioxins as we got closer to our incinerator and power plants." Thus was Dow's combustion theory born.

The company dispatched scientists to several cities to collect soil samples around municipal incinerators and powerhouses. In almost every case they found dioxin, although not necessarily 2,3,7,8-TCDD. They analyzed the carbon soot inside mufflers collected in Detroit and found dioxins. They also found 100 ppt of 2,3,7,8-TCDD in the soot from a fireplace, which happened to belong to Kagel.

According to Kagel, the formation of dioxins is maximized and its destruction minimized when the temperature is low, below 750 °C. At

Agent orange had far less dioxin than earlier 2,4,5-T herbicides used in Vietnam war

Code name	Herbicide	Quantity, gal	Period of use	2,3,7,8-TCDD, ppm
Orange	2,4-D; 2,4,5-T	10,646,000	1965–70	1.98
White	2,4-D; picloram	5,633,000	1965–71	—
Blue	Cacodylic acid	1,150,000	1962–71	—
Purple	2,4-D; 2,4,5-T	145,000	1962–65	32.6[a]
Pink	2,4,5-T	123,000	1962–65	65.6
Green	2,4,5-T	8,200	1962–65	65.6
TOTAL		17,705,200		

a Assumed level from one known and four probable samples of purple. Note: Pink and green levels are twice that of purple because they were full-strength 2,4,5-T. Sources: Proceedings from 2nd Continuing Education Conference on Herbicide Orange, May 1980; and Air Force OEHL technical report on toxicology, fate, and risk from agent orange and dioxin, October 1978

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Road going through Times Beach, Mo., is blocked by sign warning of dioxin

temperatures above 1000 °C just the opposite occurs—formation is minimized and destruction maximized. Thus, municipal incinerators could be expected to produce more dioxins than industrial incinerators, which burn at 1000 °C, because the municipal facilities operate at generally lower temperatures.

Dow Chemical researchers sample Tittabawassee River for dioxin near the company's Midland, Mich., plant

While it was doing this work Dow also was perfecting its analytical techniques, Kagel says, using a mixture of three different methods during the course of study. The first separated out 2,3,7,8-TCDD plus 16 other tetra isomers; the second, 2,3,7,8-TCDD plus 11 others; and the third 2,3,7,8-TCDD plus two other isomers. Then in late 1978 a technique was developed that isolated all 22 tetra isomers.

Since 1979 Dow has done several other studies. Having, as Kagel says, "made the comment that we thought that dioxin had been around since the advent of fire" and figuring that wood was one of the earliest fuels, a study was done of residential wood-burning stoves in Minnesota, New Hampshire, Oregon, and Michigan's upper peninsula. The source of the wood for each stove was carefully documented to make sure it had never been sprayed, never treated with pentachlorophenol, Kagel says. But in each case some dioxins were found in the soot from the stoves.

As Kagel points out, one of the components of wood is lignin, a phenolic material. There is also a natural chlorine content in wood which will vary from 14 to 84 ppm. "Remember," he says, "we're talking about reactions that occur with a yield of 10^{-10}%. These are trace reactions, and 14 ppm, when you're looking at a millionth of a millionth—a ppt—is a lot of stuff. It's the same with coal, which actually has a much higher chlorine content than wood, and is nothing more than a whole mess of ring compounds of one sort or another. So the basic building blocks are there."

"This is as close as we can come," he says, "to confirming the de novo principle, that dioxin is made from carbon, hydrogen, oxygen, and chlorine. Nobody has done a definitive experiment on that that I know of. But the preponderance of evidence right now would support the fact that you can get dioxins formed at very low levels in the combustion processes from common fuels."

If that is true it would go some way towards explaining the results of a recent study which shows dioxin contamination in fish in many rivers in Michigan. The fish were collected from 19 Michigan rivers, plus Saginaw Bay and Lake Erie by DNR. Their skinless fillets were analyzed by Swiastolov Kadzmar, a graduate student working under Matthew J. Zabic, professor of entomology and assistant director of Michigan State University's pesticide research center. Thirty-four of the 62 fish analyzed had no detectable levels of dioxin. Levels of 2,3,7,8-TCDD in the other fish samples ranged from a low of 17 ppt, with a detection limit of 12 ppt, to a high of 586 ppt, with a detection limit of 81 ppt. Many of the positive samples came from fish taken from waters that had no connection with the Tittabawassee rivershed and therefore they could not have been contaminated by Dow's effluent, though the samples did come from rivers in industrialized areas.

Typically, Kagel says, dioxin is very tightly bound to fly ash, as it is to soil. To remove dioxin from fly ash one has to do exhaustive benzene or toluene soxhlet extractions for 24 hours. "It's very tightly held," he says, "so the question is how does it get off the fly ash and into the fish?" Dow has been involved with EPA's Duluth, Minn., lab in a joint study designed to answer that question. Duluth supplied some carp fingerlings, Kagel explains, "which we put into a fish tank with some municipal fly ash of which the 2,3,7,8-TCDD content was about 160 ppt. That represented about 0.48% of the total tetra isomers, all of which were present. After 30 days in the tank the fish

Few regulations aim specifically at dioxin

Despite all the problems—medical, political, and social—associated with dioxin, it remains a remarkably unregulated compound. Early concerns focused on exposure to the dioxin-contaminated herbicide 2,4,5-T; only recently has dioxin itself been regulated.

In 1970 a Congressional hearing took place and the National Institute of Environmental Health Sciences announced a study that showed birth defects in animals that were exposed to 2,4,5-T containing low levels of dioxin. This prompted the U.S. Department of Agriculture to disallow most uses of the compound, permitting use only on forests, rights-of-way, open rangeland, and rice fields. In addition, a voluntary agreement by 2,4,5-T makers limited dioxin concentrations to less than 0.1 ppm.

The ball was passed to the new Environmental Protection Agency, which continued its investigations and soon moved to further limit the herbicide's use. In 1973, EPA set up the Dioxin Monitoring Program to monitor residues of dioxin in human and environmental samples. EPA attempted to cancel all uses of herbicides that were derived from 2,4,5-trichlorophenol in that year but eventually had to cancel the proceedings because the analytical methods necessary to determine low levels of dioxin were not available. The agency began a rebuttable presumption against registration process on 2,4,5-T in 1978.

Then in May 1979, on the basis of heavily criticized studies linking the spraying of forest areas with 2,4,5-T to a number of miscarriages among women in Oregon, EPA issued an emergency suspension that allowed the herbicide to be used just on rangeland and rice fields because EPA saw little risk of human exposure there.

The hearings on cancellation of 2,4,5-T have dragged on. They currently are suspended while EPA and the chemical manufacturers try to reach some kind of agreement, possibly on permitting some use of the herbicide if dioxin levels in it can be kept very low.

But other tools have passed into EPA's hands for regulating dioxin. On May 19, 1980, EPA published a rule under the Toxic Substances Control Act that requires any person intending to dispose of wastes that contain dioxin, or even of substances produced on equipment that previously was used to make 2,4,5-trichlorophenol, to notify EPA 60 days in advance of such disposal. That notification must include details on the amount being disposed of and the method to be used.

Just recently, the agency proposed a regulation for treating dioxin-contaminated waste under the Resource Conservation & Recovery Act. This would permit disposal of dioxin-contaminated waste only at facilities that are fully licensed by EPA. The agency says potential problems might arise if disposal is allowed at unpermitted landfills or in incinerators that might not be working properly. This rule, if adopted, would supersede the 60-day notification rule.

The other area in which EPA is moving forward is dioxin contamination of water. EPA presently is monitoring effluents from chemical plants to determine if dioxin is present and, if so, at what concentration. These data could be used in preparation of a water quality criteria document. This would give manufacturers an idea of what EPA thinks is a safe level for dioxin in water and probably would presage further regulation of dioxin, under either the Clean Water Act or TSCA. (Because dioxin is a priority water pollutant, some states have regulations that require no detectable levels in plant effluents.)

The only other significant action taken on dioxin is by the Food & Drug Administration. A series of recommendations (not regulations) by FDA in 1981 advised people not to eat fish with dioxin levels greater than 50 ppt, but that fish with less than 25 ppt of dioxin were okay to eat. Because these are not regulations, an FDA spokesman points out that if the levels do rise above 50 ppt, the agency cannot take any action to remove the product.

Thus, aside from the restrictions on the use of 2,4,5-T (because of its dioxin contamination) and the current 60-day notification rule for waste disposal, dioxin is not specifically regulated by the federal government.

were taken out and analyzed and 84% of what was found in the fish was 2,3,7,8-TCDD."

Kagel theorizes: "There's some weird mechanism in the fish—that was phase two of our study, to try and find out what that mechanism is—that makes them selectively accumulate 2,3,7,8-TCDD, or, the other way around, there is some mechanism whereby they break down or metabolize the other isomers. That was a preliminary experiment and we were going on to controlled experiments when all of this started and we never got back to it. . . . I sure would like to get an answer."

So would everybody else. Dow says that it has no manufacturing operation anywhere in the U.S., including Midland, that has any 2,3,7,8-TCDD associated with it. But EPA's Region V office in Chicago isn't so sure. On April 11 it asked Dow for any and all process- and waste-related information the company might have pertaining to dioxins. Dow delivered the first set of data—2000 pages worth—on May 12. The company said it took 26 employees, 13 of them working full time, to compile that information and it is still collecting data.

Among the data submitted were the results of a new soil analysis conducted by Dow, repeating the analysis done in 1978, except this time the analytical technique was isomer specific. Five soil samples collected inside the plant site showed levels of 2,3,7,8-TCDD of 0.08, 0.38, 2.04, 0.018, and 0.02 ppb. The levels in two samples from Midland were 0.0016 and 0.0072 ppb; Chicago, 0.0010 and 0.0042 ppb; Lansing, Mich., 0.0030 ppb and not detected; and Detroit, 0.0036 and 0.0021 ppb. "There is no health hazard in Michigan because of dioxin in the dirt or in Chicago. Not at the levels we find it," Kagel says.

Midland's mayor Joseph Mann agrees. "So what if we've got 7 ppt in the soil here. Being bound the way it is how do you get to it? How do you come in contact with it? How do you assimilate it?" He points out that if the exposure were causing harm it would manifest itself somehow. But he says studies by the State Department of Public Health have shown that "the overall cancer rate in Mid-

land is low—below the national average, below the state average, and below the average for the surrounding region." He says there was a soft-tissue sarcoma in women that was higher than normal. "There was one case in the 1950s, five cases in the 1960s, and eight cases in the 1970s. This was a matter of concern to the county health department, the state health department, and certainly to us," Mann says. The State Health Department conducted a study and released its results on May 4. And according to Mann "could not ascribe any particular causes to the rate of increase. There was no commonality between the cases that could be found; although the department felt there must have been a commonality, they certainly couldn't say that it was dioxin."

The department did recommend development of a registry of persons most likely to be exposed to dioxins as evidenced by their occupations, fish consumption patterns, or location of residence. Such a cohort of people, it said, could serve as a framework for possible future epidemiologic studies.

Meanwhile, Midland's attitude to the dioxin issue is expressed in a variety of ways. Mann says that "the perception within the community is that there's nothing out of the ordinary, nothing dangerous." But he adds, "That's not the perception if you get more than 100 miles away from here and have gotten most of your information from the news media."

Then there are the retirees from and employees of Dow who come into Rep. Donald J. Albosta's (D.-Mich.) local office and who, says office manager Pat Casey, feel as if the criticism is being directed at them. "Their feelings, and I think their beliefs, are that they worked for a high-class company that spent a lot of bucks on environmental concerns and research. Dow has always had a very aggressive in-plant safety program. So the employees don't feel there is any justification for the insinuation they pick up that Dow has done something wrong."

City manager Clifford Miles thinks that one of the reasons for the very low level of concern in the city, and one he personally subscribes to, "is

C&EN staff photos

Kagel: dioxin dust on a bookshelf

that the people who have done the testing, the measuring, the toxicology and epidemiology studies are all Midland people. They all live here with their families. It isn't some outsiders coming in and saying either it's safe or unsafe. It is Midland people that are doing these things and they have significant reputations not only in Midland but worldwide." Certainly no one is going to stay here if they know their family is in jeopardy, he says. Miles explains that over the years, because of Dow's environment and safety record, "people have built up a wealth of confidence in that corporation that could not be bought." And he says, "They [Dow] have done everything they can and should have done to alert the public, the media, the state and federal government."

Mann: nothing out of the ordinary

Some people aren't so confident. As Dianne Herbert, one of the leaders of ECOMM, sees it, "Dioxin is a sexy issue that has gotten the attention of the media, but it certainly isn't the only environmental or health problem in Michigan." She also thinks it's good that the attention of EPA is focused on Midland. However, she notes the city itself is fighting any investigation. "They naturally want to get the focus off," she says. "Their strategy is let's spread it out and say, 'Oh yes, dioxin needs to be looked at, but all over the country.' There are problems—people don't want to move to Midland, people have called and asked, 'What kind of place is it?' Maybe the problems should have been taken care of earlier on. They accumulated until they all blew up and that's too bad. I'm from Michigan and I like living here. I don't want to give up my house. I don't want to move."

Herbert says she understands the reluctance of any community to believe that there is something wrong or that the company that many of them work for has done something that is illegal or bad for their health. "The average person you talk to," she says, "will say that Dow has been good to us and I would never disagree with that. For a community this size to have its own symphony, a beautiful center for the arts—that is very unusual. But I don't think that gives them the right to do what they want with the air, and the water, and the land. The bottom line is that in this community Dow decides what is safe and what is dangerous. They make those decisions for people and I think that people should be allowed to make their own decisions."

Others are seeking further information. That was the purpose of a late May forum on dioxins organized by the Midland sections of the American Chemical Society, American Institute of Chemical Engineers, and Sigma Xi.

At the forum, which about 500 people attended, a panel of five technical experts on dioxin issues

answered questions from five local citizens—none of whom worked for Dow—and the audience.

According to Susan Butts, a senior research chemist at Dow and an organizer of the forum, its impetus came from the fact that "we were aware that a lot of studies had been done on various aspects of the dioxin problem, but we hadn't really heard very much about the results of those studies. Our concern was really in trying to hear a more detailed explanation of the situtation, in terms that would be understandable not only to scientists but to the general public." In putting the panel together, she says, "We tried to be sure that we fairly represented all points of view. We did rather heavily weight it towards people with a biomedical background, because we thought most of the questions from the audience would concern human health problems. And most of them did. There were a lot of questions about the toxicity of dioxins, about the meaning of toxicity, and about how dioxins would be rated relative to other health hazards."

For her part, Butts says she never had a personal concern about her own health, but she did want to know where Midland stood in relation to other places in the U.S. that have problems with dioxin contamination. "I felt quite reassured," she says, "by what we were told by the panel members. There were some minor disagreements about interpretation of data. But, if I were going to try to summarize what the panel said, it would be that they didn't feel that there was any significant health problem in Midland. But until we know more about the situation they would like to continue monitoring health in Midland to make sure."

In fact just about everybody seems to agree that what is needed is continued monitoring and more study, preferably not just in Midland, nor even just Michigan, but nationwide. Rep. Albosta is seeking funding for just such a study. He feels that a number of questions need to be answered. Questions such as: How pervasive is dioxin? At what concentration is it present in the environment? Where is it coming from? What are safe levels? Are dioxins bioaccumulating in the environment? Is that a problem? And, finally, are national standards needed to deal with the problem?

The study as now planned would be run by the Region V office. A prototype study costing $2 million to $3 million would first be done in Michigan. That study then would be expanded to a national level at a total cost of about $12 million. According to Richard Powers of DNR's toxic chemical evaluation section, the Michigan part of the study, as tentatively planned, would consist of a study in the vicinity of Midland to determine the extent of contamination in that area. This would mean sampling soil, air emissions, and water effluents from the plant site, and river sediments. The second component of the study would be monitoring fish, including game fish and bottom-feeding carp, in 15 Michigan rivers for dioxin contamination.

As part of the national study, air and soil sampling and possibly fish monitoring would be done at other sites, perhaps in Michigan, perhaps in Region V, or perhaps somewhere else in the country. Powers says, "It doesn't make any difference to us where they're done, as long as they are done. We feel it is necessary to have comparability studies in other areas of the country, both areas that would be expected to be contaminated and others which should be relatively clean."

Protocols for the study are being developed, but actual work is pretty much on hold because everything is contingent on getting federal funding. The House Appropriations Committee has included $5 million in EPA's fiscal 1984 funding bill for nationwide dioxin studies—$1 million for R&D and $4 million for monitoring studies in Michigan and Missouri as well as other places. The Senate Appropriations Committee has not yet made a decision. EPA's new administrator, William D. Ruckelshaus, is expected to ask Congress for more money for the agency both in this and the next fiscal year and reportedly has expressed his support for a national dioxin study.

Although everybody, including Dow, supports a study, not everybody is happy about what is being planned. As Mann puts it, "First you say there's a ticking time bomb, a life-threatening situation, and then you do these studies—the results of which won't be out for two or three years. What we need is a reasonable amount of analysis in a reasonable amount of time, primarily to reassure people outside this community that it isn't as bad as had been pictured."

Along the same lines, the Midland City Council, three of whose five members, as well as Mann, work for Dow, passed a resolution expressing its support of scientific studies on exposure levels and effects of dioxin on the environment and the public health as long as they weren't limited to Michigan, but also expressing the council's feeling that $12 million was just too much.

Further study is quite probably the proper response to the levels of dioxin contamination that have been found in Michigan. And, although EPA appeared to rush into Missouri in an attempt to improve its public image when everything the agency did was being looked at with cynical eyes, hindsight may show the decision to be justifiable and prudent. Other human exposures to dioxin, such as those of soldiers in Vietnam or the people in Seveso, Italy, in 1976, involved considerably less dioxin than those of the Times Beach residents.

In Vietnam, for instance, the Air Force's Young calculates that the level of dioxin in the soil would have been 0.017 ppb, 20,000 times less than the 300 ppb found in Missouri. That assumes that agent orange, with an average dioxin concentration of 2 ppb, is sprayed at a rate of 3 gal per acre and that all the dioxin falls right to the forest floor (although studies found that only about 7% of the agent orange penetrated the forest canopy).

Similar types of exposure comparisons can be made for the residents of Seveso, leading to the conclusion that the Missouri experience may represent the largest, long-term exposure to dioxins that humans have endured. If dioxin is the hazard that some believe, then the costs of moving entire towns probably are not greater than the risks of letting people continue to live there. □

Dioxin's Human Toxicity Is Most Difficult Problem

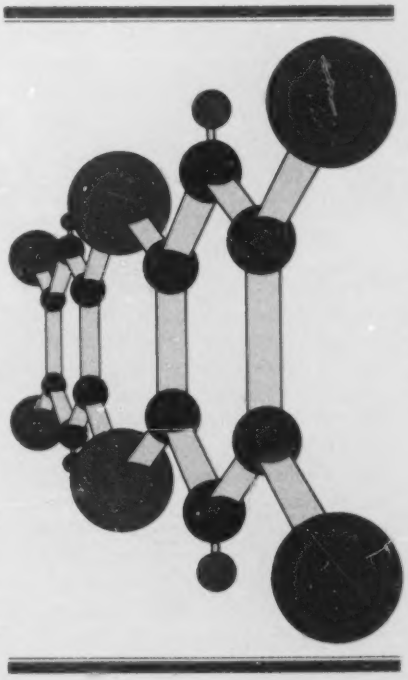
Dioxin is extremely toxic to certain animals, but scientists are only beginning to understand the nature of its toxicity and exactly what it does to humans

Rebecca L. Rawls, C&EN Washington

Of all the questions that surround dioxin, probably the most important one, and one of the most difficult to answer, is: What is its effect on human health? Although its presence in the environment still would cause problems if it were harmful only to horses or guinea pigs or some other animals, it is the possibility that dioxin may be very hazardous to people that is behind most efforts to understand how the compound behaves in the environment and to learn how to deal with it.

That dioxin is extremely toxic to certain animals, causes many different toxic effects in a wide range of animal species, and is harmful to humans when they are exposed to relatively large amounts of it are facts that are well established. But even after more than a decade of intensive study, scientists are only beginning to understand how dioxin causes its toxic effects, and the key question of whether it causes any long-term, irreversible health effects in humans remains unanswered.

The widely made claim that dioxin is one of the deadliest substances known, or that it is the deadliest man-made substance, is based on its extreme toxicity in guinea pigs. As little as 0.6 μg per kg of body weight given orally will kill half of the male guinea pigs that receive the dose. Illness occurs immediately and death within about a week. Mole for mole,



this makes dioxin some 2000 times more toxic than strychnine, for example, in the mouse. Only a handful of substances are known to be more toxic than dioxin is in guinea pigs.

But dioxin is much less toxic to mice than it is to guinea pigs. In fact, one of the striking features of dioxin's toxicity in animals is that the lethal dose varies so much from one species to another. The guinea pig, the most sensitive animal yet tested, is 5000 to 10,000 times more sensitive than the hamster, the least sensitive animal yet tested. Rabbits, mice, and monkeys cluster somewhere in the middle—roughly 200 times less sensitive than guinea pigs and 50 times more sensitive than hamsters.

Dioxins are not the only compounds that show this range of sensitivities from one animal species to another. Such a pattern is characteristic of several halogenated aromatic compounds, including chlorinated dibenzofurans and chlorinated and brominated biphenyls. The fact that all of these compounds have closely related chemical structures leads some toxicologists to study them as a class and has led to promising work that is beginning to unravel how these compounds cause their toxic effects.

Dioxins and these other halogenated aromatic hydrocarbons cause many different effects simultaneously in treated animals, and the relative importance of these effects varies from species to species. Thus, dioxin appears to kill rats by causing severe liver damage, but in the guinea pig the liver lesions seem less serious and the animal appears to die from a starvationlike wasting away of the entire animal. Both the liver lesions and the wasting away occur to some degree in all of the animals that have been studied; only the relative importance of these effects varies. Similarly, all species studied lose lymphoid tissue, particularly from the thymus, and become more sensitive to infections. However, it

usually is not the infection that kills them, and putting treated animals in a germ-free environment will not save them.

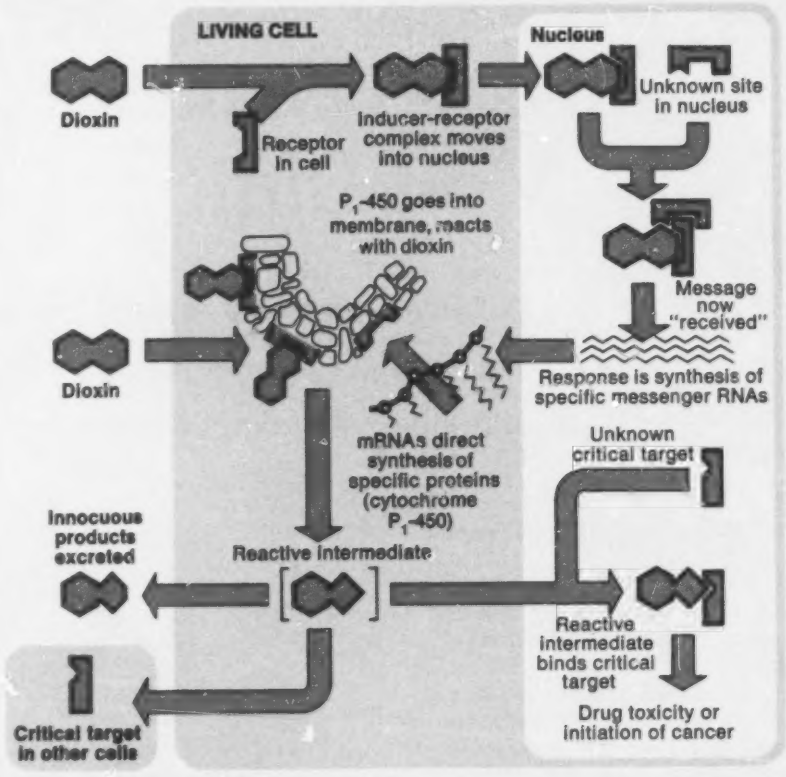
Not all effects are found in all animals. Chloracne, a skin lesion that is the most characteristic and frequently observed effect of chlorinated aromatic hydrocarbons on humans, does not occur in guinea pigs, hamsters, or some mice. Hairless mice, however, do develop a chloracnelike skin condition when exposed to dioxin, and so do rhesus monkeys and rabbits. Cattle develop skin lesions, too, but they are quite different from the kind that are seen in humans, monkeys, and rabbits.

In addition to these acute, or immediate, effects, dioxin produces at least two types of serious long-term effects in some laboratory animals—reproductive effects and cancer. As is true for nearly all long-term health effects studies, most of the work on dioxin effects has been done on rats and mice.

Because dioxin is so acutely toxic to many adult laboratory animals it is difficult to examine its teratogenic and reproductive effects. However, several studies in mice have found cleft palates and kidney abnormalities in offspring of animals fed 1 to 3 ng of dioxin per kg of body weight per day. Rat studies do not show birth defects. Instead, dioxin kills the developing fetus or embryo at levels similar to those that cause birth defects in mice.

Small-scale studies on monkeys show that dioxin is fetotoxic to these animals as well. Pathologist James P. Allen of the University of Wisconsin medical school has found that breeding female monkeys fed 1.7 ng of dioxin per kg of body weight per day for two years aborted four of seven pregnancies. In a study by Wilber P. McNulty of the Oregon Regional Primate Research Center, pregnant monkeys were given doses ranging from 9.5 to 240 ng per kg of body weight per day for three weeks during their gestation period. The two animals in the highest dose group died from their dioxin exposure. They also aborted. At the level of 48 ng per kg per day, the mothers were only slightly sick, but three of the four animals in the study aborted. At the lowest level, the mothers appeared normal.

Researchers seek to explain dioxin's effects on cellular biology



If the exquisite sensitivity of some, but not all, animals to dioxin is a frustration to many researchers, it is a source of delight to one group: the molecular pharmacologists. It is not an accident that some cells are incredibly sensitive to dioxin, and by exploiting the differences between dioxin response in different types of cells, these scientists have a probe for examining some of the very intricate inner workings of cells.

"If morphine addiction weren't a problem, morphine would still be an interesting drug for what it can tell us about enkephalins. That's the way we feel about dioxin," explains one researcher in the field.

A consistent picture of some of dioxin's interactions with animal cells is emerging from work going on in several laboratories including those of Alan Poland and Joyce C. Knutson at the University of Wisconsin; Robert A. Neal and William Greenlee at the Chemical Industry Institute of Toxicology, Research Triangle Park, N.C.; and Daniel W. Nebert at the National Institutes of Health, Bethesda, Md. Though this work does not explain all of dioxin's toxic effects, it does begin to make some sense out of one of the more puzzling aspects of dioxin's toxicity—the great range in acute toxicities found in different animal species.

According to this picture, dioxin is only one example of a larger class of halogenated aromatic hydrocarbons. All of these materials bind to the same receptor, a soluble protein within the cytoplasm of susceptible cells. The binding site of this receptor has been quite well mapped out. Substrates need to be generally planar and pretty well fill a rectangle 10 Å long and 3 Å wide. Highly polarized groups, like chlorine atoms, need to be in at least three of the four corners and nowhere else in the molecule.

These requirements fit dioxin exactly, but other molecules like chlorinated dibenzofurans or brominated biphenyls also can be accommodated in this attachment site and induce dioxinlike toxicity in animals. The site's geometry goes a long way toward explaining why the 2,3,7,8-tetrachloro isomer of dioxin is the most toxic, since this is the one that has all four corner positions of the

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molecule and no others occupied by chlorine atoms.

Once bound, the dioxin-protein complex moves into the nucleus where it turns on the activity of a specific set of genes called the *Ah* (for aromatic hydrocarbon) locus. These genes, in turn, produce messenger RNAs that direct the synthesis of a family of proteins called cytochrome P-450s within the cell. Cytochrome P-450s are enzymes whose function is to react with foreign molecules like dioxin so they can be metabolized and eventually excreted from the body.

To this point, the system seems to be a beneficial one for the cell. Unfortunately, among the metabolites of dioxin as it is processed by the cytochrome P-450 system there seems to be a substance that is toxic. Inadvertently, a system that was intended to rid the body of foreign chemicals by making them easier to excrete has converted a fairly innocuous substance into a toxic one.

It now seems apparent that this whole process is controlled genetically at two points, at least. One of these is the *Ah* locus, which controls the amount and structure of the receptor protein within the cell and turns on production of the cytochrome P-450s. Experiments in mice have shown that genetically inbred strains that do not have the *Ah* locus are not susceptible to some of dioxin's toxic effects. But the *Ah* locus alone is not enough to produce toxicity, as is shown by experiments in which cytochrome activity is turned on by the presence of dioxin though there is no toxic response. Poland and Knutson have found that chloracne can be produced by dioxin in a certain strain of hairless mice even though mice generally do not show this reaction to dioxin. It is not the lack of hair itself that is responsible for chloracne in these mice, they find. Instead, some part of the genetic locus that is responsible for the hairless trait in mice is also necessary to produce the chloracne response.

It is interesting to speculate on why animals have evolved an elaborate system for dealing with foreign chemicals and why it sometimes goes awry with molecules like dioxin, making them more, rather than less, toxic to cells. One model that satisfies pharmacologists considers dioxin to be a foreign molecule that just happens to fit into a receptor and turn on a cell system originally designed to respond to an endogenous molecule and that once had some useful purpose. Such a model makes dioxin analogous to morphine, which stimulates a natural pain-killing system in place of the body's own trigger molecule—enkephalin. But to have dioxin fit a similar pattern, there would need to be a structurally related compound naturally present, at least on occasion, in the body. There also would need to be some advantage in certain circumstances to triggering the ordinarily toxic responses that the body makes to dioxin.

The body's response to dioxin, theoretically, at least, might sometimes be useful. Properly controlled, the ability to stimulate cell proliferation, for example, could lead to useful growth or repair of tissues instead of cancer. So far, however, a natural dioxinlike molecule has not been found in animal tissue.

Useful as this picture of dioxin's role in cellular biology is, it does not explain all the chemical's toxic effects. Indeed, the model purposely focuses on those effects of dioxin that vary most widely from species to species. But dioxin has other effects, like the wasting away of tissue, that appear to be common to all animal species examined. Tissue wastage is not a trivial effect of dioxin; it is probably the cause of death in the very sensitive guinea pig.

British studies in the mid-1970s showed that animals recovering from dioxin exposure had unexpectedly high numbers of cells with more than one nucleus, suggesting that perhaps cell membrane proliferation had been impaired by dioxin exposure. This work might provide a clue to the wasting effect dioxin has on animals.

Certain experiments indicate that some of dioxin's effects are brought about by such incredibly small doses of the compound that the number of molecules in the dose is too small to account for the observed effect—at least in terms of a receptor binding model. In these cases, at least, there seems to be some sort of chain reaction that magnifies the effect of a small dose of dioxin.

peared to be healthy, and their abortion rate, one in four, was about the same as that of the nontreated group, where three abortions occurred in 11 pregnancies.

Clearly, dioxin is fetotoxic to some animals and causes birth defects in others. However, its high toxicity to the mother means that the range in which it causes toxic effects on the fetus but not on the mother is very narrow. Thus, some toxicologists classify dioxin as a weak teratogen. Ironically, the fact that humans appear to be less sensitive to the acute effects of dioxin means that it could be a more potent teratogen for them than it seems to be for laboratory animals.

Several independent tests in rats or mice show that dioxin is an extremely potent carcinogen in these animals. Richard J. Kociba of Dow Chemical's Toxicology Research Laboratory found that female rats fed 10 or 100 ng of dioxin per kg of body weight developed a greatly increased number of liver tumors. At the higher dose level, both male and female rats developed increased numbers of tumors in the mouth, nose, and lungs, as well as in the liver. Nearly half the female rats in the higher exposure group developed tumors. When the data on female rats are used to calculate the potency of dioxin as a carcinogen, dioxin comes out to be about three times as potent a carcinogen as aflatoxin B_1, which is one of the most potent carcinogens known. Equally significant, however, according to Kociba, is the finding that at doses below 10 ng even the female rats showed no increased incidence of tumors in this study. He considers this evidence that there is a no-effect level for dioxin-induced cancers in the rat.

A similar study conducted for the National Cancer Institute by researchers at Illinois Institute of Technology found statistically significant increases in thyroid tumors in male rats at all doses studied and an increase in subcutaneous tissue fibronomas in male rats at the highest dose level (0.5 mg per kg of body weight per week). In female rats, the study found an increase in tumors of the liver, subcutaneous tissue, and the brain at this same dose level.

Besides these two studies there

2,3,7,8-Tetrachlorodibenzo-p-dioxin is a crystalline solid at room temperature

have been about a half-dozen others that provide some evidence that dioxin is a carcinogen in rats and mice. Although some of these other studies have methodological flaws that make them less definitive than either the Kociba or the NCI study, a panel evaluating the carcinogenic potential of dioxin for the Environmental Protection Agency in 1981 concluded that collectively these studies support the conclusions of the Kociba and NCI studies and provide strong evidence that dioxin is a potent carcinogen in animals.

Most chemical carcinogens tend to attack specific organs and produce large increases in one particular type of tumor. Dioxin produces many different tumor types in different organs, which has led some researchers to speculate that it may be a promoter, rather than an initiator, of carcinogenicity. In other words, dioxin might not actually be responsible for tumor formation, but might instead work in some way that makes the cells more receptive to tumor formation if some other activating agent is present to begin the process.

Several studies have been designed to consider this possibility. One, by Henry C. Pitot and coworkers at the University of Wisconsin, examined the effect of dioxin on rats that already had been exposed to another carcinogen, diethylnitrosamine. Animals receiving both substances had a greatly increased incidence of liver tumors compared to those that received dioxin alone, suggesting that dioxin can be a promoter of carcinogenicity. However, in a series of studies by D. L. Berry of Oak Ridge National Laboratory's biological division, dioxin neither initiated nor promoted carcinogenicity when administered along with polycyclic aromatic hydrocarbon carcinogens. Instead, it appeared to block the effect of these carcinogens in mice.

Dioxin's chemical structure suggests that it could intercalate into DNA as several carcinogen initiators are believed to do. However, experiments designed to show such interaction have, so far, given only negative results, possibly because the molecule is so highly reactive with cellular proteins that it is not actually available to react with DNA. The highest estimate of the degree of covalent bonding of dioxin to rat liver DNA in vivo is less than 1 molecule of dioxin per 10^{11} nucleotides, or four to six orders of magnitude less than what is found for most chemical carcinogens.

As is almost always the case in dioxin research, the interpretation given to these and other animal test findings depends very much on who is making the interpretation. To Dow Chemical's director of biomedical research, James H. Saunders, the animal data show that dioxin is a promoter, but not an initiator, of carcinogenicity in animals. The EPA carcinogen assessment group, on the other hand, says that since promoters generally do not produce the large increases in tumor formation when given alone that dioxin produces, dioxin should be regarded as both an initiator and a promoter of carcinogenicity.

The differences in interpretation given to the animal data on dioxin toxicity, however, pale almost to insignificance when compared with the differences that arise from examining the human data. All of the data on humans come from people who somehow have been inadvertently exposed to dioxin, always in combination with many other halogenated aromatic chemicals, and often in situations where the exposure occurred years or even decades before anyone realized that it might have important health consequences. As a result, such basic information as exactly who was exposed to dioxin at what concentration and for how long often can only be estimated.

As with animal studies, the acute effects of dioxin exposure are the easiest to establish. Most of these data come from industrial accidents in which a fairly small number of workers received a single exposure to dioxin. There have been more than 800 reported cases of this type of exposure. In addition, some 37,000 people may have been exposed to measurable amounts of dioxin when a 2,4,5-trichlorophenol-manufacturing reaction went out of control at the ICMESA chemical plant near Seveso in northern Italy. More than 500 residents of nearby towns were treated for what were presumed to be toxic effects following the accident. Thus, Seveso stands out as the single most important industrial accident in terms of the information it can provide about the human health effects of dioxin.

By far the most significant finding from the Seveso data and those of the other industrial accidents is that humans are much less sensitive to the immediate toxic effects of dioxin than are guinea pigs. So far, there has been no clear case of a human death caused by dioxin exposure, discounting voluntary abortions that were performed following the Seveso accident. There are, however, many well-documented toxic effects.

The bellwether of these acute effects is thought by many epidemiologists to be chloracne, a skin condition in which circular patches of blackheads and pale yellow cysts develop on the face and, in more severe cases, on other parts of the body.

More than 800 workers have been exposed to dioxin in industrial accidents

Date	Workers exposed	Location of accident	Remarks
1949	250	Monsanto's 2,4,5-trichlorophenol plant at Nitro, W.Va.	122 cases of chloracne being studied; so far, 32 deaths vs. 46.4 expected; no excess deaths from malignant neoplasms or circulatory disease; studies continue
1953	75	BASF's 2,4,5-trichlorophenol plant at Ludwigshafen, West Germany	55 cases of chloracne, 42 severe; 17 deaths so far vs. 11 to 25 expected (4 gastrointestinal cancers and 2 oat-cell lung cancers); most common injuries were impaired senses and liver damage; studies continue
1956	?	Rhône-Poulenc's 2,4,5-trichlorophenol plant in Grenoble, France	17 cases of chloracne, also elevated lipid and cholesterol levels in blood
1963	106	NV Philips' 2,4,5-T plant in Amsterdam, the Netherlands	44 chloracne cases (42 severe), of whom 21 also had internal damage or central nervous system disturbances; 8 deaths so far (6 possible myocardial infarctions); some symptoms of fatigue; full report planned
1964	61	Dow Chemical's 2,4,5-trichlorophenol plant at Midland, Mich.	49 cases of chloracne; deaths so far 4 vs. 7.8 expected, 3 cancer deaths vs. 1.5 expected, one a soft-tissue sarcoma; studies continue
1965–69	78	Continuing leaks in 2,4,5-trichlorophenol processing area of Spolana's 2,4,5-T plant near Prague, Czechoslovakia	78 cases of chloracne; so far 5 deaths; many of the 50 workers studied for more than 10 years have hypertension, elevated blood levels of lipid and cholesterol, prediabetes; significant amounts of severe liver and neurologic damage; studies continue
1966	?	Rhône-Poulenc's 2,4,5-trichlorophenol plant in Grenoble, France	21 chloracne cases
1968	90	Coalite & Chemical's 2,4,5-trichlorophenol plant in Derbyshire, U.K.	79 chloracne cases; so far 1 death from coronary thrombosis; cohort study planned; company refuses to divulge any more information
1976	156[a]	ICMESA's 2,4,5-trichlorophenol plant at Seveso, Italy	Workers are being studied along with exposed townspeople; more than 500 residents treated for presumed toxic symptoms; 134 confirmed chloracne cases; overall mortality rate normal so far; studies continue

a In addition to these ICMESA workers, some 37,000 residents of nearby towns also were exposed to dioxin in this incident. **Source:** American Medical Association study, 1981

By itself, chloracne is not considered a serious condition, although it can be disfiguring while it persists. After mild exposure it usually clears up in a few months, but for more severe cases it can last for as long as 15 years. Hundreds of cases of chloracne have been seen after industrial accidents, including 134 confirmed cases at Seveso. Most of the Seveso cases were elementary school children.

In addition to chloracne, other symptoms develop with increasing dioxin exposure. These include a general sense of fatigue or malaise, disturbances in the responses of the peripheral nervous system such as a measurable slowing down of the speed at which nerve impulses travel through the limbs, and liver toxicity including changes in many enzyme levels and in some cases enlargement of the liver. Industrial exposure data seem to indicate that these conditions generally disappear after a few years and the experience at Seveso seems largely to confirm these findings.

Of more concern at Seveso and elsewhere are the possible chronic effects, especially those that might be caused by lower-level exposures like those experienced by soldiers serving in Vietnam during the 1960s when dioxin-contaminated herbicides were used there, by workers in plants making dioxin-contaminated products and by their families, by citizens living in communities like Times Beach, Mo., with its unexpectedly high levels of dioxin in the soil, or even by the population of areas where 2,4,5-T or other dioxin-contaminated herbicides may have been used during the long period when such use was allowed in the U.S. Potentially exposed people in these categories easily number in the hundreds of thousands.

Fortunately, the evidence for chronic health effects in humans is much less substantial than for acute effects. There are, in fact, distinguished researchers who argue that no chronic human health effects of dioxin have been proved. Stated just that way, probably few epidemiologists would disagree. But there are studies that suggest long-term health problems and literally thousands of anecdotal incidents that link dioxin exposure to health problems.

Probably the most highly respected studies suggesting a link between dioxin exposure and long-term health effects are those of Swedish epidemiologist Lennart Hardell at University Hospital, Umea. Hardell's work links use of dioxin-contaminated phenoxy herbicides with an increased incidence of soft-tissue sarcomas, a rare form of cancer that affects muscle, nerve, and fat tissue. In two studies he finds a five- to six-fold increase in the incidence of this type of tumor in people who have used phenoxy herbicides compared with his control group.

Dow scientists, and others, have criticized the Hardell studies on several counts. For one thing, the determination of whether or not

subjects were exposed to phenoxy herbicides was made by asking them or their relatives whether they could remember any exposure. This is not a very accurate method, and, according to Dow's Saunders, people in the exposed group more frequently were asked if they could recall herbicide use than were people in the control group. Another point that concerns epidemiologists is that the people in one study apparently were exposed to products that contained much lower levels of dioxin than those in the other study, but both groups showed the same degree of increased risk. Such data suggest that some factor other than dioxin might be responsible for the elevated cancer risk. Finally, there is a problem with the identification of the tumors as soft-tissue sarcomas. Because this is a rare cancer type, most pathologists have very little experience in identifying it. It is, to some degree, a classification that is used for tumors that don't fit into other, more clearly definable categories. Hardell relied on medical records to identify the sarcomas; he did not examine the tissues himself.

Nevertheless, the Hardell studies cause concern, and that concern is increased by early results from studies of Monsanto and Dow Chemical workers who were exposed to dioxin in separate industrial accidents in 1949 and 1964. Altogether, 182 workers from these two incidents are being monitored. By 1979, 36 of these workers had died, fewer than the 54 that would have been expected based on national mortality statistics. However, three of the people who died had soft-tissue sarcomas, and a fourth who has died since 1979, also had soft-tissue sarcoma. For a form of cancer with a predicted incidence of less than 1% among cancer victims, finding four in such a small sample is unexpected. "It certainly raises the question as to whether there is something there," says Dow's Saunders. "But, [although] it is statistically significant, there is always that uncertainty of what would have been the luck of the draw in a sample this small."

Examination of death certificates and hospital records for Midland County, Michigan, where Dow's plant is located, also shows an elevated incidence of soft- and connective-tissue cancers among women in the period from 1960 to 1978. Exactly what this finding means is unclear, according to a report from the Michigan Department of Public Health released last month.

"It is not my judgment at this point that there is a clear link [between dioxin exposure and incidence of soft-tissue sarcomas in humans]," Saunders says. "It is a question that merits further study. We do not see sarcomas in animals [exposed to dioxin]," he points out. "What we see are carcinomas, [which are] epidermally derived tissue tumors, particularly liver cancer, as in the rat. Furthermore, when one sees cancer in rats, one sees it at a level 10 times that which produces obvious toxicity in the animal. In other words, when one produces liver cancer with dioxin in the rat, one has a very sick rat who is very sick for a long time and then develops cancer." This is very different from the humans who develop soft-tissue sarcomas, he maintains.

Other studies do not show an association between phenoxy herbicide use and increased incidence of soft-tissue sarcoma. One study that examined the relationship among people in various occupations in the state of Washington and incidence of soft-tissue sarcoma found that the occupations with the greatest number of soft-tissue sarcomas, as determined by data on death certificates, were marine engineers and bankers, groups that would not be expected to have had particularly high exposure to dioxins. Allan H. Smith and associates at the school of medicine at Wellington Hospital, New Zealand, are in the midst of a study of the incidence of soft-tissue sarcomas among herbicide applicators in New Zealand. Because New Zealand requires herbicide applicators to be registered, records of exposure to phenoxy herbicides are particularly good in that country. In a preliminary report presented in 1982, Smith had not found any instances of soft-tissue sarcomas in this group.

The Veterans Administration is putting together a study designed to see if Vietnam veterans, who may have been exposed to dioxin through the use of agent orange in Vietnam, have an increased incidence of soft-tissue sarcomas. The study, being directed by epidemiologist Han K. Kang, will use data from the Armed Forces Institute of Pathology, which is, in effect, the U.S. center for the evaluation of soft-tissue sarcomas. The institute has on file some 8500 cases of soft-tissue sarcoma, or roughly one quarter to one third of all the cases ever reported in the U.S. The study will examine tumors reported to the institute between 1975 and 1980 to see if Vietnam veterans are overrepresented in this group. A final report of the study is expected in 1985.

One potential problem with this study is that the latency period for soft-tissue sarcomas is thought to be about 15 years. Since dioxin contamination of Vietnam occurred in the 1960s, the time period may be too short to evaluate properly what effect dioxin use in Vietnam had on development of this type of tumor. However, by 1980, reports of Hardell's findings were causing pathologists to look more closely for soft-tissue sarcomas, and the researchers chose a 1980 cutoff to remove this bias from their study.

In addition to cancer, animal studies raise concern about the possibility of fetotoxicity in humans exposed to dioxin. Several studies and many anecdotal reports of such effects in humans have appeared. By and large, however, these studies have methodological flaws that bring their findings into question.

One of the most important of these studies, at least politically, involved a group of nine women in the Alsea

Dioxin's lethality compared to other poisons

Substance	Animal	Minimum lethal dose (moles per kg body weight)
Botulinum toxin A	Mouse	3.3×10^{-17}
Tetanus toxin	Mouse	1.0×10^{-16}
Diphtheria toxin	Mouse	4.2×10^{-12}
2,3,7,8-TCDD	Guinea pig	3.1×10^{-9}
Bufotoxin	Cat	5.2×10^{-7}
Curare	Mouse	7.2×10^{-7}
Strychnine	Mouse	1.5×10^{-6}
Muscarin	Cat	5.2×10^{-6}
Diisopropylfluorophosphate	Mouse	1.6×10^{-5}
Sodium cyanide	Mouse	2.0×10^{-4}

Source: EPA

Basin in Oregon who lived near forests that were sprayed seasonally with dioxin-contaminated herbicides. The women were concerned that 13 miscarriages in their group in the mid-1970s seemed to be linked chronologically with the spraying of the forests. The Environmental Protection Agency conducted two studies, one examining just these nine women and a larger one looking at miscarriage rates in that part of Oregon. Although the first study did not find a statistical relationship between the women's miscarriages and the spraying, the second study did. This study played a major role in EPA's decision in 1979 to issue an emergency suspension against many uses of the dioxin-contaminated herbicide 2,4,5-T.

However, the study did not stand up to critical evaluation. A team of University of Oregon researchers in 1979 panned the study on practically all counts. Among other things, they found that the study did not have a proper control, its data both on miscarriages and on 2,4,5-T spraying were inaccurate, there were many other factors besides 2,4,5-T spraying that varied among the three groups examined, and the variations in the levels of miscarriages reported by the study were well within expected ranges.

Poorly designed or conducted studies seem to plague the effort to find out if dioxin causes human reproductive effects. At least two Vietnamese studies, one from the early 1970s and one announced earlier this year, claim to show a substantial increase in these conditions as well as cancer following the spraying of agent orange in that country. However, western epidemiologists are uncomfortable with the lack of data on normal rates for miscarriage and birth defects in the Vietnamese population. They also question the way in which the Vietnamese data were collected.

Similarly, data from Seveso seem to show an increase in both the number of spontaneous abortions and in the number of birth defects in the period immediately following the ICMESA accident. However, there is so much uncertainty about what levels should be considered normal for this population that it is unlikely that the question of whether the Seveso incident caused increases in these conditions will ever be resolved. Epidemiologists who think there may be an association between dioxin exposure and these effects call the Seveso data "suggestive" of an effect; those who think that these effects probably don't occur in humans point out that the levels were well within the normal range for western countries.

There exist, in addition, several studies that do not show any increase in miscarriages or birth defects among populations that might be considered at risk because of their dioxin exposure. Studies of Dow Chemical and Monsanto chemical workers and their wives show no increase in either of these factors. So does a study released last month by the Michigan Department of Public Health that examined the rate of birth defects in Midland County, where Dow made 2,4,5-trichlorophenol until 1979.

A recently released study of the reproductive effects of dioxins on the families of Australian soldiers who fought in Vietnam during the period when agent orange was being sprayed there shows no increase in miscarriages or birth defects among these families. The study is highly praised scientifically, but there is uncertainty as to whether these Australian soldiers received very much exposure to dioxin while they were in Vietnam. Consequently, this negative finding does little to allay the fears of those who think dioxin may cause human reproductive problems.

So the overall picture that has emerged so far shows dioxin as extremely toxic and carcinogenic based on animal studies, but the picture is much less clear about human health effects. Human studies are continuing—the U.S. government is spending more than $100 million on several epidemiologic studies of the health consequences of possible dioxin exposure to veterans who served in Vietnam, and major studies also are under way in Australia, New Zealand, Finland, Sweden, the U.K.,

Dioxin's lethal dose varies in different species

Animal	LD_{50} (μg per kg body weight)
Guinea pig	1
Rat (male)	22
Rat (female)	45
Monkey	<70
Rabbit	115
Mouse	114
Dog	>300
Bullfrog	>500
Hamster	5000

Source: Poland and Knutson, *Annual Review of Pharmacology & Toxicology*, 1982

Dioxin has different effects in different animals

Symptom	Monkey	Guinea pig	Cow	Rat	Mouse	Rabbit	Chicken	Hamster
Abnormal cell proliferations or organ enlargement								
Gastric mucosa	++	0	+	0	0			0
Intestinal mucosa	+							++
Urinary tract	++	++	++	0	0			
Bile duct/gall bladder	++		+		++			
Lung				++				
Skin	++		a	0	0	++		
Atrophy or decreased cell proliferation								
Thymus	+	+	+	+	+		+	+
Bone marrow	+	+			+		+	
Testicle	+	+		+	+		+	
Other effects								
Liver lesions	+	0		++	+	++	+	+
Edema	+	0		0	+		++	+

Note: 0 indicates lesion not observed; + indicates lesion observed (number of pluses notes severity). a Skin lesions are observed in cattle, but they are different from the lesions seen in other species. Source: Poland and Knutson, *Annual Review of Pharmacology & Toxicology*, 1982

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and many other countries. Most of the U.S. studies are scheduled to be completed by 1987, but already epidemiologists wonder whether uncertainties about exposure levels and questions about what other factors may have accompanied dioxin exposure will weaken the value of the studies' findings.

Not surprisingly, current assessments of the risk dioxin poses to human health vary greatly depending on which of the available data seem most important to the assessor. A reasoned argument can be made that the animal data show, in addition to severe toxic effects in certain species, that great variability can be expected from one animal species to another and that the available human data suggest that humans are among the least sensitive of animals to dioxin's effects. That interpretation is not incompatible with any of the human epidemiologic data published so far, and it may turn out to be the true picture of dioxin's hazard.

Most toxicologists, however, are much more conservative in their risk assessment. This means that, in the absence of stronger evidence to the contrary than has been seen so far for dioxin, a proven risk in animals is considered to be a potential risk in humans, and a substance that causes acute effects in humans is viewed with suspicion as a possible cause of chronic effects.

It is in this spirit of prudence that EPA views the cancer risk of dioxins in humans. "Carcinogenic responses have been induced in mice and rats at very low levels of [dioxin]," EPA's carcinogen assessment group concluded in 1981. "In addition, dioxin has been shown to be a potent cancer promoter. These results, together with the strongly suggestive evidence in epidemiologic studies, constitute substantial evidence that dioxin is likely to be a human carcinogen."

Such assumptions are only the first step in coming up with an estimate of human risk in any particular situation, however. At a site like Times Beach, Mo., explains Renate D. Kimbrough, medical officer for the center for environmental health at the Center for Disease Control, assessors also need to know how much dioxin people exposed to contaminated soil

C&EN staff photo

Saunders: experimental uncertainty

are likely to absorb. That's not well established, she says, although one study at the University of California has shown that when dioxin is on the skin, 1 to 10% will be absorbed. Dioxin binds to soil, so probably less is absorbed from there than if the dioxin were applied directly to the skin. One Seveso study found that about 1% of soil dioxin was absorbed, but the sample size was small and the results are inconclusive.

Besides, Kimbrough points out, absorption may not be the only route of exposure. Some contaminated dust may float in the air and enter the lungs, and some may be eaten, especially by children.

Given all these uncertainties, CDC still came up with a level of soil contamination that it believed was low enough to pose no threat to the health of Times Beach residents. "We decided to take one increased incidence in a million as a reasonable risk," Kimbrough says, and to base their hazard assessment on studies of birth defects caused by dioxin in rhesus monkeys. Toxicologists usually allow a factor of 100 below the no-effect level in an animal study as a margin of safety when extrapolating to humans, she explains. However, in the case of the monkey study, the animals had limited, not lifetime, exposure to dioxin, so the standard safety factor was increased to 1000. The resultant calculations come up with 1 ppb as a level likely to be safe. A similar calculation based on the carcinogenicity of dioxin in rats gives about the same level, Kimbrough says.

Such values ought not to be taken as a national standard for dioxin in the soil, she cautions. CDC will be reviewing its assessment procedure with outside consultants to see if it is possible to come up with national standards for soil contamination. Even if such standards can be drawn up, there is not likely to be a single level that will be appropriate for all sites, she points out. For example, in desert areas, where very few people live, soil probably could contain higher levels of dioxin before the total health risk became equivalent to the one at Times Beach. On the other hand, data from the U.S. Department of Agriculture indicate that grazing livestock easily pick up dioxin from the soil, probably because they eat so much soil as they graze. People who eat the meat from these animals or drink their milk have an additional route of exposure to dioxin. Thus, soil levels in areas where animals graze must be lower to obtain an equivalent risk.

Is it really appropriate to base human health risk estimates on the experience of laboratory animals when limited data suggest that humans may be a good deal less susceptible to dioxin than some laboratory animals are? Kimbrough thinks it is. There is very little information on what chronic exposure levels have been in workplaces, she points out, so it is difficult to know how much weight to place on long-term studies of workers' health that seem to find no ill effects. Also, except for Seveso, there is very little information on the effects of dioxin on women or children. And even at Seveso, soil dioxin levels in areas where people were allowed to return to their homes were generally in the parts-per-billion range or lower. Animal studies show that dioxin's effects vary greatly from one species to another. In some cases the effects have even been pinned down to the presence of a particular genetic locus within a species. But the human population is genetically very diverse, so that even if many people are not susceptible to the hazards of dioxin, there may be subpopulations who face a substantial risk. □